THE GENERAL THEORY

OF

CANCER-FORMATION.

BEING

A LECTURE DELIVERED AT THE CANCER HOSPITAL ON MARCH 1ST, 1889.

BY

HERBERT SNOW, M.D.LOND., ETC.

SURGEON TO THE HOSPITAL.

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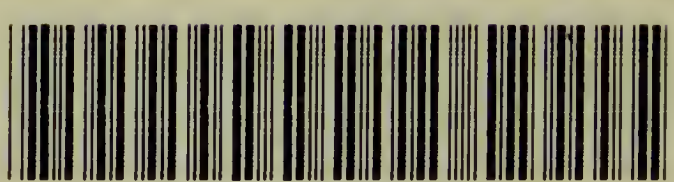

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In this Lecture an attempt is made to present a concise general survey of the various cancerous diseases, according to their natural relations; together with a reasonable and not altogether unpractical theory of the mode in which all arise. The word "cancer" is used throughout in its popular sense to include the whole group.

6, Gloucester Place,
Portman Square;
October, 1889.

CLASSIFICATION OF THE CANCEROUS DISEASES.

I. Cancer originating in the cells of *Pavement epithelium* . . } Epithelioma.

II. Cancer originating in the cells of *glandular epithelium* . . {
- Scirrhus, Encephaloid } (Practically identical varieties of the same disease).
- Cylindroma (C. of tubular gland follicles).
- Lympho-sarcoma (C. of lymph-glands; not to be confounded with lymphadenoma [Hodgkin's disease]).

III. Cancer derived from the cells or corpuscles of *connective tissue* . . . . . } Sarcoma.

(Sub-varieties)—Spindle-celled.
Round-celled.
Myeloid.
Glioma.

IV. Cancer derived from *endothelial* plates (cells) . . } Endothelioma.

V. Secondary varieties resulting mainly from *degenerative processes* in some of the preceding . . . .
  - Colloid.
  - Melanoid.
  - Osteoid.

VI. Cancerous diseases in which either the malignant process is ordinarily less acute than in the foregoing, or in which malignancy supervenes on some other morbid process as a secondary feature. The first two belong to the class of epithelial neoplasms; the remainder appear to rank as sarcomata .
  - Rodent ulcer (cancer of hair follicles).
  - Xeroderma pigmentosum (Kaposi).
  - Intra-cystic growths.
  - Myxoma.
  - Keloid (primarily benign, often secondarily becomes cancerous).
  - Chloroma.
  - Granuloma fungoides (T. Fox).
  - Molluscum fibrosum. (A rare form of spindle-sarcoma of the skin has been included under this title; although the designation should properly be limited to a non-malignant disease. See 'British Medical Journal,' October 31st, 1885.)

THE GENERAL THEORY

OF

CANCER-FORMATION.

In the two lectures which I am now to have the honour of delivering, I propose to lay before you, first of all, my conceptions of the general theory of cancer-formation,—of the fundamental generative process which I assume to lie at the root of all the varieties of malignant disease, which binds these into one strongly marked group, and at the same time obviously differentiates them from every other class of neoplasms. Then, subsequently to discuss, so far as time will allow, the details of structure, and the various clinical phenomena shown by these special forms of new growth; resulting, as I hold, from the operation (I may not say the violation) of but one natural law. First, then, as to the general theory of cancer.

I need hardly remind you that our bodies are wholly composed of cells, pure and simple, of modified cells; and of products formed within cells. That the simplest type of an animal organism is the amœba, which consists of but a single cell, and yet maintains an independent existence.

As you are well aware, the amœba consists (or is spoken of as consisting) of a jelly-like substance called protoplasm. I say "is spoken of as consisting" because in the properties of this protoplasm lies concealed the mystery of life, because we are utterly unable so far to solve that mystery, or to explain the enormous differences in vital phenomena evinced by cells absolutely identical to our senses, and to all the tests we can at present apply; and so, because the term covering so much that is unknown—covering, it may be, an extremely complex and heterogeneous organisation—is at present little more than a mere verbal designation, of provisional convenience; a stepping stone, we will hope, to higher things.

The amœba, like every other cell, has (or has had) a nucleus; that is to say, a small portion of the protoplasm is differentiated from the rest—has higher vital and different chemical properties—and acts as a sort of governing centre to the whole. There is, in some individuals, but not in all, a further differentiation of *ectosarc* and *endosarc;* that is, of cell-wall more compact, and of cell-contents softer and more fluid.

Now, this little body exhibits, on a microscopic scale, all the phenomena of the largest member of the animal kingdom. It takes food into its substance, digests it, excretes the useless portions; it moves about, the contractions of its body which produce such motion taking place either in response to direct irri-

tation by contact with a foreign body, or to governing forces acting from within; it reproduces its kind by fissiparous division (this probably commencing in the nucleus, as a rule); and lastly, it may be said to breathe, the metabolic changes which nourish it being largely processes of oxidation.

All cells, again, are fundamentally constructed upon the same ground-plan as the amœba, and all (through some portion of their existence, if not the whole) behave in an exactly similar manner as regards not only the ordinary vital processes, but also their capacity for independent movement. In our own blood at this moment, as I need hardly remind you, are a large number of organisms which are to all intents and purposes amœbæ, and which play a most important part in all pathological processes, especially in that of which I have now to speak.

I must first, however, mention that the cell-type, like all other types, is subject to manifold variations. The most important perhaps of these is the differentiation of cell-wall from cell-contents; not constant, and not well marked in the amœba, this is most evident in the Vegetable Kingdom; in the Animal, it is never so distinct as in plants, and is often altogether wanting. Particularly is such the case with the cells of malignant tumours; which cells are manifestly aberrant from their proper functions, and tend towards reversion, rather than to specialisation and evolution.

Again, many cells have several, or even numerous nuclei; and hence abundant varieties in the reproductive phenomena. I will ask you to adopt (for the moment, at any rate) my own conception of the nucleus and of its relations to its cell. The whole being regarded as a jelly-like mass of protoplasm, the nucleus is simply a highly differentiated portion of the same, of different chemical properties (as evinced by the effects of staining agents), probably connected with a higher oxygenation. Like the brain in our bodies, it is a governing centre, regulating the vital properties of the rest of the organism; and if dead or removed the latter is dead also. But it is still only a specialised and differentiated portion of the lump of jelly aforesaid, and any portion of the latter may apparently become thus differentiated; so there may be only one or many nuclei, arising independently of each other, and subsequently proceeding to an independent life-history as separate cells. In most of the cells composing the animal body, and especially in those which constitute cancerous tumours, we do not see any trace of that regular fissiparous division of cell and nucleus, which takes place in vegetable cells, nor do we see any defined cell-wall; in most of the latter there is not even indication of such a structure. But we do find, as a general rule, a great abundance of nuclei, and these tend to attain an enormous size, as compared with that of the primitive cell, or with the remaining

bulk of the malignant cell; so that, at one time, this huge nucleus was considered pathognomonic of, and special to, cancer. We can now, however, only regard it as an indication of exuberant growth.

Now, the cells (at one period in their existence amœbæ to all intents and purposes) which compose our bodies have, of course, undergone further development into the various tissues, nerve, muscle, bone, &c. But a certain proportion attain no higher organisation, and it is among these, or their descendants, that cancer-growth almost (if not indeed quite) invariably takes its rise. And so, all the essential phenomena of cancer are phenomena only of cell-growth, cell-development, and cell-decay.

Cancers naturally fall, according to their origin from three species of cells, into three typical classes. We have thus: 1. The malignant tumours or deposits originating from epidermis or epithelium, from the cells coating skin or mucous membrane. 2. Those from the secreting cells (also sometimes described as epithelium, and practically identical therewith) of glands. 3. Those from the cells or nuclei of connective tissue. Those of the first kind are ordinarily spoken of as Epithelioma; of the second, as Carcinoma; of the third, as Sarcoma. Endothelial plates also appear occasionally to develop cancerous new growths, but such are of extreme rarity.

Now, the first step towards the genesis of a cancer

is the presence of an exciting cause. We need not here discuss the question of predisposing causes, and I may say that I have little faith in those ordinarily assigned. In the first class (the Epitheliomata) we can, under average circumstances, trace out the direct operation of the former, which may be summed up as long-continued mechanical irritation. Cancer of the lip or tongue (to take an ordinary example) commonly arises from long-continued chafing by the sharp projecting point of a broken tooth, or by a warm pipe-stem rubbing against some tiny crack or fissure;—whereby the surface-cells gain access to, and become, as it were, planted in, a new soil, the submucous or subcutaneous tissue. Some such fairly obvious excitant is never absent.

In cancers of the second class, of the secreting glands, the exciting cause is somewhat more difficult to trace, but still, by patient investigation, can almost always be discovered. In a certain proportion of instances, it is mechanical, as in the epitheliomata, but then usually takes the form of a sudden blow, not of continued irritation. (The effect of both, however, is probably identical; the natural boundary or basement membrane being in the latter case ruptured by the sudden violence, the secreting cells gain access to the underlying and more or less devitalised tissues, in which they find a congenial nidus for exuberant growth).

In the great majority, however, the cause is neurotic, and acts through the medium of the central nervous system; in other words, mental depression, worry, &c., are the great generators of cancer of this variety; and the female, the more neurotic and emotional sex, are by far the principal sufferers from it. You well know how dependent the function of most if not of all the secreting glands is upon the central nervous system, and its varying conditions. Familiar examples are; neurotic diarrhœa; the phenomenon of the "draught" in the nursing mother, the excitation of the salivary glands by the odour, or even the idea, of savoury food; the dry, parched mouth (on the other hand) caused by terror; and so on.

In the Sarcomata, cancers of connective-tissue origin, the exciting cause is often almost impossible to find; and one reason for the obscurity of cancer causation in general, is the chronic course of the disease in many instances, the malady arising a long period of years before the patient comes under our observation. These last, however, appear to originate in some mechanical injury, often extremely slight, and of which all memory (supposing even that there has been more than a passing sensation) is speedily lost;—usually a blow or muscular strain. A typical example of the above was lately in the hospital, in the shape of an originally strong and finely built man of thirty-five years of age, with multiple cancerous tumours on

the abdominal wall. These belonged to the disease sometimes described as "Molluscum Fibrosum," being round, soft, pedunculated masses, many of which were now ulcerated: under the microscope, the section presented the characters of ordinary spindle-celled sarcoma. They had repeatedly recurred after extirpation, and the patient was now going downhill very fast. But the new growths had first commenced more than twenty years previously, and the man's own idea of their mode of production was that "they began after he had missed his kick at football." I may remark that, in seeking to investigate the commencement of a malady whose genesis is so commonly enveloped in mystery as cancer (and especially as sarcoma), it is important not to lose sight of very slight lesions or injuries, however apparently disproportionate to the effect ultimately produced. The works of Darwin have well taught us the exceeding value of the most seemingly insignificant trifles in the mind's eye of a great observer.

So all cancer originates from irritated protoplasm, such irritation being either direct or (perhaps more frequently) indirect through the medium of the central nervous system; and I believe the condition of the latter to exert a powerful influence, not only as regards the genesis of the new growth, but also upon its subsequent course and phenomena.

The stimulated cells then proceed to grow and

proliferate, quite independently and apparently more or less at the expense of, the remainder of the organism. At first the advance is often extremely slow and insidious; in the end, it is apt to be extremely rapid and exuberant, although, of course, there are many exceptions. And not only does the parent neoplasm thus act, but cells and cell-germs are eventually broken off and carried away, either by the lymph or blood current, to distant parts of the body; wherever these lodge, they grow and flourish in the same manner as the primary cancer. Very various processes of decay and degeneration ultimately ensue, both in the primary and secondary tumours; these we shall consider subsequently if time permit.

In the microscopical specimens which Dr. Dove, our pathologist, has placed upon the table, you will see examples of the different classes of malignant tumour; and will notice the cells, whatever may have been their respective origin, proliferating more or less exuberantly at the expense of the surrounding tissues. Here, however, comes in a very important factor, both in the life-history of the several kinds and also in the appearances which these present under the microscope. For according partly to their origin, partly (in however a far less degree) to idiosyncrasies of construction in the body of each individual, the proliferating cells prey upon the surrounding structures (more especially upon the white fibrous tissue) with

much greater facility in some cases than in others; and accordingly as the original framework of the part is preserved for a longer or shorter time, do we see in the microscopic section the phenomena of cell-growth pure and simple; or of these mixed with the appearances resulting from the disposition of normal structures. As an example, the acinar or alveolar appearance said to characterise the very familiar scirrhus cancer, is simply the result of cell-growth in the interstices of rigid and resisting connective tissue, which as you know normally forms an irregular stroma. If the latter be succulent and easily devoured by the cancerous cells, no such feature is visible, or only in a minor degree; and the tumour is termed "soft cancer," "encephaloid," or "medullary." (The most typical cancer-acini are formed on a basis of pre-existing adipose tissue: the process is shown in this diagram.)

In the female breast we see every gradation between the two extremes here noted; at one end of the scale, abundant fibrous tissue, typical acini; at the other little or no fibrous tissue, exuberant cell-development, combined with rapid cell-degeneration. The microscopical appearances vary greatly at different parts of the same tumour, and again at different stages of its development; but, as I have said, appear fundamentally to depend most of all on the age and idiosyncrasies of the individual patient; the old, spare, and

"tough" inclining to the former; the young, florid, and fat to the latter.

In estimating the significance of microscopical appearances there is one point however which must not be lost sight of. I allude to the law by which like produces like—the child resembles the parent—and the new (cancerous) cell tends to resemble its parent (non-cancerous) cell, not only in visible shape, but also in mode of growth, and of relation to its environment. The most typical example of this is, perhaps, the Cylindroma, sometimes (very improperly) termed "Columnar epithelioma." I say improperly, because columnar epithelium, *per se*, has nothing whatever to do with the genesis of the morbid growth in question. Columnar epithelium is very abundantly distributed throughout the body, whereas cylindroma is found only in one or two localities—*par excellence*, the rectum. It occurs only where *tubular follicles* are met with; its essential feature being the reproduction, with aberrant and malignant characters, of *tubular gland structure*.

Another instance is Rodent Ulcer, which results from proliferation of the small epithelioid cells lining the root sheath of the hair. Under the microscope, sections display small, irregularly branched, and inosculating columns of similar small epithelioid cells, which are growing in number and bulk at the expense of the intervening tissues; the disease is, in fact, a cancerous reproduction of *hair follicles, minus* the hair.

And the rare "Thyroid cancer" affords another remarkable example.

All malignant neoplasms probably show in their early stages this resemblance of the new to the parent tissue; in some, as in many spindle sarcomas, it is maintained throughout their whole career; but on the other hand, in some almost from the beginning, in most, towards the later phases, the exuberant cell-development (with its concomitant rapid decay); and the tendency of the cells to revert to an embryonic type,—entirely obliterate it. So that, when a malignant growth has attained an advanced period of development, the question of its origin is frequently a mere matter of guesswork. The term "sarcoma," I imagine, is at the present day commonly thus used (very conveniently indeed) to designate tumours whose derivation has thus become obscure. On the evidence of the microscopic appearances alone, it is in fact extremely difficult to classify with certainty, almost any malignant tumour, which has attained a large size; especially when situated among the viscera.

If we examine individual cells from a fresh specimen of cancer, we see only evidences of rapid proliferation, such as would be found in any rapidly growing protoplasm. Apart from their exuberant growth, and tendency to decay rather than to undergo higher organization, we are utterly unable to discover any *special* characteristic, which may be said to place

them on a different footing from their immediate progenitors, or from other cells, non-cancerous. Yet I need hardly remind you that, *in its clinical phenomena*, cancer lies very widely apart from every other disease, or from every other kind of new growth.

[*Note.*—It is not, of course, meant to imply that the benign and cancerous neoplasms do not occasionally closely approach each other in histological structure, or that a tumour may not show malignant features in one part, together with a perfectly innocent reproduction of normal tissues at another. The spindle-celled sarcoma displays very varying degrees of organization, when we contrast one specimen with another, or even when we compare different portions of the same; and some examples differ but slightly from the tumour wholly composed of well-organised, and therefore non-cancerous, fibrous tissue; so that these would seem to have commenced as benign growths, wherein the cancerous process has been developed secondarily. Intra-cystic growths in the mamma present a very common and unimpugnable example of the supervention of malignancy in a structure primarily innocent; and often so continuing for a long period of years. All that it is intended here to convey is that this process, when established, whether among old or newly-formed tissues, stands entirely apart from, and is incapable of comparison with, any other pathological phenomenon or series of phenomena.]

The most salient point which I wish to lay before you, which accounts for the inefficiency of drugs, and which lies at the root of all the other great practical difficulties in the path of the surgeon who has to deal with this horrible disease, is that when once these cells, these little masses of protoplasm, have been so far irritated that the malignant proliferation commences, and they have begun to assume this quasi-independent vitality, —nothing, short of actually destroying the cell, will arrest the process; and they behave as independent organisms, refusing allegiance to the laws which regulate the rest of the system. Through some break-down, probably in the nervous, regulating, and inhibitory apparatus, which links so many heterogeneous units into one body, one harmonious machine, these tiny creatures (if I may so speak) revert to their primary amœbiform condition, and live, not only on a separate footing from the remainder of the animal, but even at the cost of the latter. They become, to all intents and purposes, parasites—parasites whose powers of self-propagation and diffusion confer on them such terrible potency of evil.

That this view is something more than mere hypothesis is shown by the curious phenomenon of *auto-inoculation*. Here we see malignant tumours arising in cavities, as the abdominal cavity, the mouth, or the larynx, give rise to numerous secondary growths, by a simple process of grafting; detached cells or

cell-germs becoming adherent to some other part of the free mucous or serous surface, in localities more or less distant, and there continuing to increase and multiply. Mr. Arnott ('Cancer; its Varieties, their Histology and Diagnosis,' 1872, pp. 13, 14) quotes several very interesting and instructive examples; but the occurrence is not a rare one; it is a matter of every-day clinical observation, and may be seen in almost every advanced case of cancerous mouth or tongue.

Lastly, I would hazard a remark, in reference to the fashionable bacterial pathology of the day, that those diseases, such as leprosy and tubercular consumption, in which an active bacillus has been discovered, appear to be on a totally different footing from the class of maladies here discussed. (In the former there has always been evidence, or, at any rate, strong suspicion of a *contagious* element; none, or none of the smallest value, in the latter). That, so far, we have no grounds whatever for expecting such a solution of the great mystery of cancer-formation. That, if I may venture what is at the best but a dim and tentative guess, this solution will ultimately be found in a better knowledge, first, of the properties of protoplasm, and of its vital phenomena, probably studied most easily in the case of the lowest unicellular organisms; and secondly, of the manner in which the protoplasmic elements of our bodies are influenced and controlled by the central nervous system.

[*Note.*—Upon two other theories of cancer-formation, which have obtained credence, a few words may be here added. Darwin's doctrine of pangenesis may be dismissed with the remarks that we do not, as a rule, find evidence of any congenital element in cancer (see paper "Is Cancer Hereditary?" in 'British Medical Journal,' October 10th, 1885, with analysis of 1075 cases). And that when we see malignant tumours originating almost always from definite and ascertainable causes in persons showing no trace of predisposition, we have no need to call in the aid of such a recondite and improbable explanation, in order to account for their presence.

The rather fascinating views of Dr. Creighton (see 'Reports of Medical Officer to Privy Council,' vol. vi, New Series) upon the production of mammary cancer, &c., require a little further discussion. According to the generally accepted view, the breast is developed from the epiblast. Creighton, on the other hand, regards it as a modified fat gland, formed in the mesoblast; its glandular and connective-tissue elements being thus histologically equivalent.

With this assumption, he attempts to show that the various forms of tumour in the breast correspond to the various states of the secreting structure, and to the varying degrees of the secretory force, as measured on the physiological scale. "In consequence of some morbid influence or diseased excitation, the

gland reacts by following the slow process of normal evolution; but as the evolution and unfolding is spurious, it is associated with the formation of peculiar, imperfect, crude, or waste cellular products, which are derived from the epithelium, and accumulate in the acini, or leave them to infiltrate the peri-acinous tissue, instead of passing out of the mamma by the lymphatics, to be converted into lymphoid cells in the lymphatic glands." Hence he ascribes the formation of morbid growths to vacuolation and metaplasia of the secreting cells, the products of which may either remain *in situ*, or may wander out of the acini, and which give rise, in accordance with the stage of evolution they represent, to carcinoma, sarcoma, myxoma, or enchondroma. In carcinoma we have a feeble secretory force, a half-roused functional stimulus. If the cells proliferate within the acinus, we have medullary cancer; if the process is extra-acinous, scirrhus. In *Myxoma* the gland reaches a late period of evolution, nearest in intensity to perfect lactation. *Enchondroma* corresponds to the same degree of excitation that affords mucus, except that a hyaline intercellular substance is formed instead of fluid.

Dr. Creighton discards altogether the doctrine that sarcoma is derived from the connective-tissue, and regards the spindle cells as merely spindle-shaped epithelial cells, growing in the peri-acinous tissue.

So far as these views can be practically tested,

the stress laid upon vacuolation, together with the diagrams by which Dr. Creighton illustrates this supposed process, does not at all accord with the experience of most other workers with the microscope. And in almost every spindle sarcoma we see the most unmistakable gradations of structure between the embryonic and the well-organised fibrous tissue, so that the connective-tissue origin of the growth hardly admits of doubt.

But, as we can by no means at present in our power gauge or measure the respective degrees of physiological stimulation, upon which the whole theory hinges; it is obvious that a large part of the field is amenable to criticism only upon general considerations. And upon this ground, the manner in which tumours of the most diverse pathological characters and clinical behaviour are here linked together; the absence of any attempt to account for the extreme rarity of some of these (myxoma and enchondroma very seldom occur as breast tumours) in contrast with the relative frequency of others; the limitation of Dr. Creighton's researches to the mammary gland, and the want of a consistent explanation as regards the phenomena of cancer-origin in other parts; seem to present insurmountable objections to it, and to debar it from any higher title than that of "hypothesis."]

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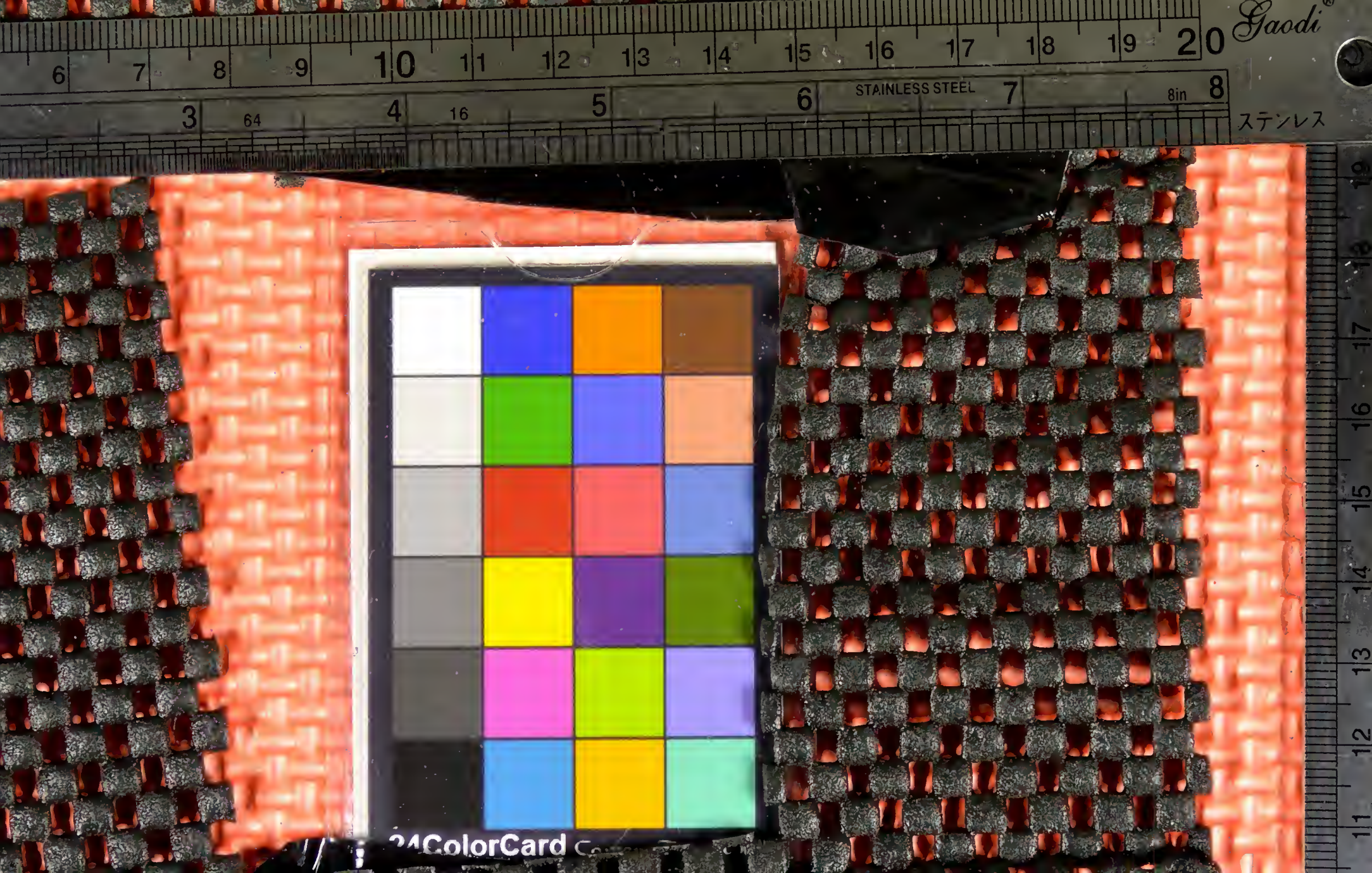
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